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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/777,488	02/12/2004	Adnan M.M. Mjalli	41305-296609	2347

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EXAMINER	
STOCKTON, LAURA LYNNE	
ART UNIT	**PAPER NUMBER**
1626	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/777,488	MJALLI ET AL.	
	Examiner	Art Unit	
	Laura L. Stockton, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,16-33,38 and 40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7-12, 16, 19, 22, 24-33, 38 and 40* is/are rejected.

7)☒ Claim(s) *6,17,18,20,21 and 23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/12/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

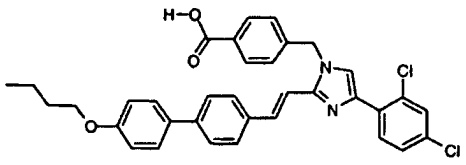
Claims 1-12, 16-33, 38 and 40 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group III (claims 1-46), and the species of Example 320 found on page 287 of the instant specification (reproduced below), in the reply filed on October 27, 2006 was acknowledged in a previous Office Action.

The structure given in the election was actually the structure of Example 320, as stated by Applicant in the Remarks section of the Amendment filed June 18, 2007.

Example 320



4-[2-[2-(4'-butoxy-biphenyl-4-yl)-(E)-vinyl]-4-(2,4-dichloro-phenyl)-imidazol-1-ylmethyl]-benzoic acid

The claims within elected Group III and the Information Disclosure Statements were examined to the extent that they are readable on the elected species of Example 320. Since no prior art was found on the elected species, the examination was expanded within elected Group III until art was found, in which case, the examination stopped and art has been applied against the claims. Note, M.P.E.P. § 803.02. The subject matter of the expanded search (inclusive of the elected species of Example 320) is as follows:

W is $N(R_2)$;

$\mathbf{Ar_1}$ is an optionally substituted phenyl;

$\mathbf{Ar_2}$ is an optionally substituted phenyl;

T is an optionally substituted phenyl;

$\mathbf{L_2}$ is a direct bond; and

all other variables are as defined.

The claims that are embraced by the subject matter of the expanded search are claims 1-46. The requirement

was deemed proper and therefore made FINAL in a previous Office Action.

Subject matter not embraced by the above indicated expanded search are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention(s), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 27, 2006.

Rejections made in the previous Office Action that do not appear below have been overcome by Applicant's amendments to the claims, including the obviousness-type double patenting rejection over copending application 11/056,498. Therefore, arguments pertaining to these rejections and objections will not be addressed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 31 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for those therapeutic agents in which specific examples are given on page 324 of the instant specification {i.e., alkylating agents, antibiotics, etc.}, does not reasonably provide enablement for DPP-IV inhibitors, GLP-1 mimetics, insulin mimetics, fibrates, biologic response modifiers, etc. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets

the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The nature of the invention

Applicant is claiming compositions that have additional therapeutic agents. However, some of these agents are not adequately described in the instant specification (i.e., DPP-IV inhibitors, GLP-1 mimetics, insulin mimetics, fibrates, biologic response modifiers, etc.).

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher* , 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to pharmaceutical compositions comprising multiple active agents, one

would need to consider drug-drug interactions. For the preparation of pharmaceutical compositions containing multiple active ingredients, one needs to take into account drug-drug interactions. For example, there are various types of anti-viral agents known in the prior art, which act by differing mechanisms such as virucidal agents, which directly inactivate viruses, antiviral agents, which inhibit viral replication, and immunomodulators, which boost the host immune response. Some of these anti-viral agents may be incompatible with applicant's compound of the formula I due to drug-drug interactions. Taking antiviral drugs with certain other medicines may affect the way the drugs work or may increase the chance of side effects. Obach {Drugs of Today, 39(5), 2003, pages 301-338} discloses that in regards to any given pharmacokinetic drug-drug interaction, the two drugs involved can be considered as either the "perpetrator" drug or the "victim" drug. The perpetrator is the drug that affects the activity

of an enzyme of protein involved in the metabolism or disposition of the victim drug. The victim drug is the one that either causes side-effects or toxicity due to increased exposure, or lack of efficacy due to exposure decreased to below that required for therapeutic effect (page 302). There are varying mechanisms of drug interactions such as the reduction in the rate of the metabolism of one drug by another, the irreversible inactivation of drug-metabolizing enzymes and the exposure to the victim drug is decreased (pages 303-304). Obach also discloses that there are a number of *in* vitro and *in vivo* experimental approaches to be taken to determine drug-drug interactions (page 304).

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present for the pharmaceutical compositions containing additional therapeutic agents is found on page 324 of the instant specification. While some of the therapeutic agents

have specific examples, some of the broad therapeutic agents fail to provide any direction or guidance as to the breadth or specific identification of these type of therapeutic agents.

The quantity of experimentation needed

The nature of the pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities for each of the diseases and disorders instantly claimed. The quantity of experimentation needed would be undue when faced with the lack of direction and guidance present in the instant specification in regards to testing all diseases and disorders generically embraced in the claim language, and when faced with the unpredictability of the pharmaceutical art. Thus, factors such as "sufficient working examples", "the level of skill in the art" and predictability, etc. have been demonstrated to be

sufficiently lacking in the instant case for the instant method claims.

The level of the skill in the art

Even though the level of skill in the pharmaceutical art is very high, based on the unpredictable nature of the invention and state of the prior art and lack of guidance and direction, one skilled in the art could not use the claimed invention without undue experimentation.

Response to Arguments

Applicant's arguments filed October 12, 2007 have been fully considered but they are not persuasive. Applicant argues that: (1) one skilled in the art at the time of filing would not need any guidance as to the breadth of these particular types of therapeutic agents or how to identify these types of therapeutic agents; and (2) the class of compounds found in instant claim 31 are well known in the art.

All of Applicant's arguments have been considered but have not been found persuasive. As stated above, the instant specification does provide examples of most of the additional therapeutic agents found in instant claim 31. However, some of the broad therapeutic agents fail to provide any direction or guidance as to the breadth or identification of these type of therapeutic agents {i.e., DPP-IV inhibitors}.

35 USC 112, first paragraph, states that the specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention. The specification must teach how to make and use the invention, not teach how to figure out for oneself how to make and use the invention. *In re*

Gardner, 166 USPQ 138 (C.C.P.A. 1970). For all the reasons given above, the rejection is deemed proper and therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7-12, 16, 19, 22, 24-33, 38 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heerding et al. {WO 2000/71120}.

Determination of the scope and content of the prior art (MPEP §2141.01)

Applicant claims imidazole compounds. Heerding et al. (see entire document; particularly pages 2-4 and 9-

11; formula (II) on page 4; and especially Examples 69-71 on page 29) teach imidazole compounds that are structurally similar to the instant claimed compounds.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the compounds of the prior art and the compounds instantly claimed is that the instant claimed compounds is a hydrogen versus a methyl group attached to the 1-position nitrogen of the imidazole ring.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

It is sufficient if a reference compound is so closely related to claimed compound that a chemist would find the difference an obvious variation; thus, claims are refused where the difference is primarily the one which exists between a secondary and a tertiary amine. *Ex parte Bluestone*, 135 USPQ 199 (1961).

One skilled in the art would thus be motivated to prepare tertiary amine compounds of the prior art to arrive at the instant claimed products with the expectation of obtaining additional beneficial products which would be useful in treating bacterial infections. The instant claimed invention would have been suggested to one skilled in the art and therefore, the instant claimed invention would have been obvious to one skilled in the art.

Response to Arguments

Applicant's arguments filed October 12, 2007 have been fully considered but they are not persuasive. Applicant argues that Heerding et al. do not teach the instant currently amended claims because the compounds in Heerding et al. have a hydrogen at the 1-position of the imidazole ring whereas the instant claimed compounds must have a substituent other than hydrogen. In response, as stated above, it is sufficient if a

reference compound is so closely related to claimed compound that a chemist would find the difference an obvious variation. The rejection is deemed proper and therefore, the rejection is maintained.

Allowable Subject Matter

Claims 6, 17, 18, 20, 21 and 23 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

This application contains subject matter not embraced by the above indicated expanded search drawn to inventions nonelected with traverse in the reply filed on October 27, 2006. A complete reply to the

final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura L. Stockton whose telephone number is (571) 272-0710. The examiner can normally be reached on Monday-Friday from 6:15 am to 2:45 pm. If the examiner is out of the Office, the examiner's supervisor, Joseph McKane, can be reached on (571) 272-0699.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

The Official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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December 31, 2007